The Effect of Modafinil on +Gz Tolerance in Healthy Male Aircrew

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Abstract

Background: Modafinil, a centrally acting alpha-adrenergic agonist, promoting wakefulness, has been approved in Armed Forces across the world for sustained Military operation.

Aim: The present study was carried out to examine the effect of Modafinil on +Gztolerance, which is of relevance in long duration tactical combat operations.

Method: A randomized, double blind placebo-controlledtrial was carried out to administer 200 mg of Modafinil or placebo to each of the participants of Modafinil or placebo group. Each group consisted of 11 healthy male volunteers. The average age, height and body weight of the participants were 24.2±3.85 yrs, 175.3±4.69 cm and 70.2±9.21 kg respectively. Standard gradual onset run (centrifuge accelerating at 0.1 G/sec)was used to assess the +Gz tolerance of the individual during both relaxed state and when they performed straining manoeuvre. A mixed between-within subjects analysis of variance was carried out to assess the impact of two different interventions (Placebo and Modafinil) on participants' Gz tolerances across four time periods (pre-placebo, post placebo, pre-Modafinil and post-Modafinil).

Results: There was a significant main effect of time ($p<0.001$) and no significant interaction effect between time and the drug was observed ($p=0.279$). Relaxed Gz tolerance was not different in the placebo group before and after its administration (3.99±0.52 and 3.90±0.52 G), but was significantly higher in the Modafinil group after its administration (3.90±0.29 and 4.07±0.52 G). An independent sample t-test was carried out to compare relaxed Gz tolerance between placebo and Modafinil group before and after the administration of the drug. Straining G tolerance was significantly higher in the Modafinil group (5.75±1.03 G) than the placebo group (5.37±0.48 G).

Conclusion: Administration of Modafinil affects+Gz response in healthy individuals.

Keywords: Modafinil, alpha adrenergic agonist, relaxed Gz tolerance, straining Gz tolerance.

Introduction

Modafinil, a wakefulness-promoting agent, was originally developed in France and was first offered as an experimental treatment for Narcolepsy in 1986. The drug was approved by US Food and Drug in 1998 [1] and was used to treat narcolepsy, shift-work sleep disorder and excessive day-time sleepiness associated with obstructive sleep apnoea/hypopnea syndrome [2-3]. Militaries of several countries have approved the use of Modafinil for extended air operations [4-5]. In the United States military, Modafinil has been approved for use in certain Air Force missions and is being investigated for other uses [6]. As of Nov 2012, Modafinil is the only drug approved by USAF to be used as a drug to manage fatigue [7]. In 2011, the Indian Air Force approved the use of Modafinil in the contingency plans [8]. It has also been reported that Modafinil had been used by the astronauts during long-term space mission on-boardInternational Space Station [9].

Modafinil administration has been reported to influence the autonomic cardiovascular activity. Markis et al

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reported an increase in Heart Rate (HR) and Blood Pressure (BP) after Modafinil administration [10]. Whereas, other scientific study reported that Modafinil intakedid not affect the autonomic cardiovascular response [11]. Modafinil has also been tried in treating neurocognitive impairment of patients with Postural Orthostatic Tachycardia Syndrome (POTS). POTS is clinically characterised by exaggerated increase in HR on assuming upright posture. The study by Kpaeyeh et al revealed that HR did not differ significantly during orthostatic stress between placebo and Modafinil group. However, the seated and standing BP were significantly higher in Modafinil treated group [12]. Additionally, administration of Modafinil also causes an increase in sympathetic neural activity and attenuates parasympathetic neural activity as confirmed by heart rate variability study along with concomitant increased levels of catecholamineslike Nor-epinephrine, dopamine, dihydroxyphenyl-acetic acid, dihydroxyphenylglycolin plasma and increased levels of nor-epinephrine and epinephrine in the urine. Despite having an increased sympathetic activity of Modafinil on heart (cardiac adrenoceptor stimulation), it has also been reported that Modafinil causes a differential sympathetic effect in peripheral tissue beds. Or in other words, Modafinil attenuates the muscle sympathetic nerve activity as confirmed by peroneal microneurographic study [13].

The contention that Modafinil administration increases HR and BP and has a strong sympathomimetic effect, it was hypothesised that Modafinil intake may confer a better protection to +Gz tolerance. During exposure to +Gz forces, the blood and body fluid is translocated to lower limb blood vessel causing a concomitant reduction in arterial blood pressure at head level. This in turn results activation of sympathetic neural system to compensate for fall in blood pressure. The inherent sympathetic activation that happens with G pooling, if coupled with Modafinil administration could prevent HR and BP, might confer better G protection. No study is available which has examined the administration of single oral dose of 200 mg of Modafinil on relaxed and straining +Gz tolerance in healthy male aircrew. The present study was undertaken to observe the impact of Modafinil administration on G-tolerance during gradual onset rate centrifuge run once in a relaxed condition and on other occasion with straining manoeuvre.

Material and Methods

22 healthy males were selected for the present study. The participants were non-smokers and occasional drinkers. They were instructed not to consume alcohol at least 48 hours before the study. Participants with any cardiovascular and autonomic co-morbidity were excluded from the study. The participants were randomly divided into two equal groups consisting of 11 volunteers in each group. One group was designated as 'placebo' group and the other group as 'Modafinil' group. The participants were explained in detail about the possible consequences of taking of Modafinil. The study protocol was approved by the Ethics committee of the Institute. Voluntary written informed consent was taken from each participant for taking part in the study.

Each participant reported to the laboratory at 0800 hours in the morning. The relaxed and straining Gz tolerances of the individuals were measured in High Performance Human Centrifuge (HPHC). The HPHC was developed by AMST, Austria (Model No. HTC-V, Human Training Centrifuge-V). The relaxed +Gz tolerance is the +Gz level at which arelaxed subject experiences Peripheral Light Loss (PLL) and while straining tolerances refers to that level of +Gz at which PLL occurs despite the subject uses straining manoeuvre to prevent blood pressure fall.

Human centrifuge usually consists of a capsule (or gondola) mounted at the extremity of a rotating arm. G varies with distance from the centre of rotation and with the velocity of the capsule as per the equation $G= v2/rg$, where G is the acceleratory force applied during rotation, v is the velocity of the gondola, r is the radius of the rotating arm and g is the acceleration due to gravity [14].

The participant was explained about the protocol of the run and how to use the 'Dead Man's Switch' while experiencing PLL during straining tolerance. For measuring relaxed +Gz tolerance, the centrifuge was rotated at the rate of 0.1G/s from baseline of +1.4 Gz. The lights inside the gondola were switched off. The LED lights bar present in front of the subject consisted of one central red light and two peripheral green lights, one at each side of the red light. LED lights were switched on when speed of the gondola picked up at +1.7Gz. The participant was instructed to fix his gaze at central red light. Through RT communication, the subject was

instructed to remain relaxed. The moment two peripheral green lights were not visible to the subject, he called out and the Gz-level of the subject was recorded at this point. This +Gztolerance was referred to as relaxed +Gz tolerance or level tolerance of the subject. The +Gz level tolerance was measured by the ability of the pilot to maintain vision or consciousness.

On second occasion, the straining +Gz tolerance of the individuals was measured following a standardised protocol followed in the Institute. They donned anti-G suit and performed anti-G Straining Manoeuvre (AGSM) during exposure to acceleration stress [14, 15]. PLL was the end point to determine straining +Gz tolerance. When the subjects reached PLL level, they released the dead man's switch and the +Gz level was recorded. This +Gz was referred to as straining +Gz tolerance.

After measuring the relaxed and straining tolerance, the participant was given either placebo or 200 mg of Modafinil randomly. The present study design was a double blind placebo controlled trial. The same study protocol was followed to measure the relaxed and straining tolerance of the individuals again following four hours of administration of the drug. The scientific literature suggests that Modafinil reaches its peak concentration in the plasma within four hours of its oral intake [16]. Hence, post-drug trial of measuring G tolerance was carried out after four hours in the present study.

Data collected was analysed by using a statistical software SPSS 20.0. Data was first checked for normality by Shapiro Wilks 'W' statistic. Continuous data were presented as the mean ± standard deviation. A between-within subjects analysis of variance was carried out to assess the impact of two different interventions (placebo and Modafinil) on the G tolerances of the individuals across four different time periods (pre-placebo, post placebo, pre-Modafinil and post Modafinil). Independent sample t-test was employed to compare the data of relaxed and straining tolerances between placebo and Modafinil groups before and after administration. The level of significance was set at $p<0.05$.

Results

Table 1 shows physical characteristics of the participants. Modafinil group had a significantly higher body height than placebo group. Table 2 shows the relaxed and straining G tolerances of individuals before and after their administration.

Table 1. Physical characteristics of the participants

Parameters	Placebo Group Mean ± SD	Modafinil Group Mean ± SD	Level of significance (p value)
Age (years)	25.5±5.07	22.9±1.37	NS
Body height (cm)	173.1±4.70	177.5±3.69	S*
Body weight (kg)	68.1±10.59	72.4±7.47	NS

NS: Not Significant; * significant p=0.025

Table 2. Relaxed and Straining Gz Tolerances in Placebo and Modafinil group before and after their administration (n=11 in each group)

Gz Tolerance	Placebo		Modafinil	
	Pre	Post	Pre	Post
Relaxed	3.99±0.52	3.90±0.52	3.90±0.29	4.07±0.52* #
Straining	5.66±0.73	5.37±0.48 **	5.90±0.68	5.75±1.03 ** ##

* / ** $p<0.05$ and $p<0.01$ Significantly different from before administration
# / ## $p<0.05$ and $p<0.01$ Significantly different from placebo group

Placebo group did not show any changes in relaxed Gz tolerance after its administration. But, Modafinil group showed a significant increase in relaxed Gz tolerance after its administration ($p<0.05$). Also, when post-intervention relaxed Gz tolerance was compared between the placebo and the Modafinil group, it was observed that the Modafinil group had a significantly higher Gz tolerance ($p<0.05$) than the placebo group.

Straining Gz tolerance decreased significantly in the placebo ($p<0.01$) and the Modafinil group ($p<0.01$) following intervention of the drugs. Further, when straining tolerance was compared between the placebo and the Modafinil group post-intervention, Modafinil group was found to have a significantly higher tolerance than placebo group ($p<0.01$).

Discussion

The present study examined the role of Modafinil administration on relaxed and straining Gz tolerances in healthy males. The result suggested that Straining Gz tolerance post-Modafinil (5.75±1.03 G) was significantly higher than post-placebo straining Gz tolerance (5.37±0.48G). Modafinil was also found to cause an increase in relaxed Gz tolerance post its administration.

Modafinil is a centrally acting alpha-adrenergic agonist and promotes wakefulness. This drug is a relatively new alertness-enhancing compound of interest to the military aviation community for long duration tactical combat operation [17]. The precise mechanism of action of Modafinil is unclear. Scientific literature suggests that Modafinil exerts their sympathomimetic action by binding directly with Dopamine and Norepinephrine receptor in the brain, thus leading to inhibition of both catecholamine transporters. Positron emission tomography imaging study found that 200 mg of Modafinil administration in human results in 51% of DAT occupancy [18]. This in turn results in elevation of norepinephrine, Dihydroxyphenylglycol (DHPG), dihydroxyphenyl-alanine(dopa) and dihydroxyphenyl-acetic acid (DOPAC) and serotoninin the plasma [2,19].

Various scientific studies have reported the increase in HR and BP on administration of Modafinil [10]. In addition to increase in HR and BP, it has also been reported that the effect of Modafinil is also reflected by an increase in sympathetic activity and attenuation in parasympathetic effect. The study on heart rate variability has confirmed that low frequency power (a measure of sympathetic neural activity) and high frequency power (a measure of parasympathetic neural activity) of heart rate variability increases and decreases on Modafinil intake [13].

Recent scientific study from our laboratory has confirmed that Modafinil administration causes an increase in HR and BP during isometric handgrip strength test when compared to the responses seen with placebo administration [20].

During performance of straining G tolerance, the individual performs an Anti-G Straining Manoeuvre (AGSM). The AGSM consists of forced exhalation against a closed glottis or a partially closed glottis while tensing leg, arm and abdominal muscles. The muscles become fatigued during performance of AGSM since they undergo contraction primarily through isometric means. Isometric contraction impedes the blood supply to the muscle during contraction phase unlike isotonic contraction. Since Modafinil administration increases the blood pressure by augmenting sympathetic neural response, there is likelihood that this may further aggravate the fatiguing of contracting muscles involved in AGSM, which may further reduce the straining Gz tolerance. This did not happen in individuals taking Modafinil in the present study. This has been perhaps made possible due to the fact that Modafinil also reduces the muscle sympathetic nerve activity in the peripheral musculature [13]. It may be possible that Modafinil had a direct or indirect peripheral effect that contributes to pressor response.

In conclusion, the present study observed a statistically significant increase in straining +Gz tolerance after administration of Modafinil as compared to placebo administration. The result of the present study suggests that Modafinil intake may thus confer better +Gz tolerance to acceleration stress in healthy individuals.

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